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SHORTER ARTICLES AND DISCUSSION

ESTIMATING THE NUMBER OF GENETIC FACTORS
CONCERNED IN BLENDING INHERITANCE

IN *Science* for July 29, 1921, Dr. W. E. Castle develops a "method of estimating the number of genetic factors concerned in cases of blending inheritance," which appears so simple, so attractively cogent, and so usable, that it is to be feared that the erroneous assumptions upon which it is based may be given less consideration than they merit.

About seven years ago,¹ I took some pains to point out certain fallacies which had crept into genetical literature through the tacit (or express) assumption that the several factors affecting the size of an organism or its parts, or the intensity of development of any character, are similar to each other in kind and equal in effectiveness. It has seemed to me that since that time there has been marked improvement in the literature dealing with this particular phase of genetical phenomena—whether in response to my paper or through independent following out of the simple logic of the case, it matters not. It comes as a distinct shock, therefore, to see the sudden reversion in Dr. Castle's paper to a supposedly outgrown and abandoned conception.

Dr. Castle has probably forgotten the bearing of my paper, though he commended it very highly in a letter written at the time of its publication; for so far as I can now recall he has never referred to it in any of his frequent papers, published since that time, on subjects involving the multiple factor hypothesis as an explanation of blended inheritance and the modification of a so-called "unit-character." This omission has been the more interesting because my paper even gave the precise interpretation of his hooded-rat case, which has been very lately espoused by him.²

Referring to the particular question now under discussion, my paper said:

Attempts to determine how many plural determiners for any quantitative character are involved in a particular cross are as yet premature. Such attempts are based on the unproven hypothesis

¹ "Duplicate Genes for Capsule-form in *Bursa bursa-pastoris*," *Zeitschr. f. indukt. Abstamm. u. Vererb.*, 12: 97-149. 1914.

² Castle, W. E., "Piebald Rats and the Theory of Genes," *Proc. Nation. Acad. Sci. [U. S. Amer.]*, 5: 126-130, 1 fig., April, 1919.

that the range of variability in F_2 equals the combined ranges of P_1 and F_1 generations, and the unwarranted assumption that the different plural determiners are essentially equal in effect.

What was premature seven years ago might be conceivably no longer premature, of course, but since the basis upon which Dr. Castle now proposes to estimate the number of such plural factors in specific crosses involves the same fallacies which made previous attempts untenable, it is needful to reiterate that nothing in the evidence justifies the belief that this new plan will give any sort of approximation to the actual facts. Nevertheless, the method proposed by Castle may be expected to have a certain amount of interest as representing a limiting case.

It is absurd to suppose that the height of a man will be as much affected, severally, by the factors which increase the thickness of the scalp, as by those which affect the length of the long bones of the legs; or that factors which produce changes in the number of internodes of a plant will generally add severally the same increment to the stature of the plant as will factors which increase the length of some or all of the internodes. Castle recognizes this weakness, but seeks to minimize its importance and declares that "no other assumption will permit of a general treatment of blending inheritance." He means, of course, merely that on no other basis can a generalized mathematical scheme be developed such as that which he has here presented.

But even if we allow such assumption of equivalence of genetic factors to pass on the ground of mathematical expediency, there are several other conditions involved in Castle's scheme which are equally unwarranted and which will profoundly affect the validity of the conclusions arrived at.

For example, the two strains mated together are supposed to stand at the two extremes of the total potential genetic variability in their progeny and all of the determiners are assumed to be additive in their effect, so that if we let the factors be represented in the usual manner by letters, the lesser parent must have the formula $XXaabbccddeeff \dots$, while the larger parent occupies the other extreme $XXAABBCCDDEEFF \dots$. It need scarcely be pointed out that while such a situation might be realized in some specific case it could not be generally true, and the greater the number of factors involved in any specific cross, the less likely would it be that the larger parent would possess them all and the lesser parent none. In my paper, referred to above, I said in regard to this point (p. 132):

Nilsson-Ehle (1911) has described a case in which the range of variation in the length of heads of wheat in the F_2 considerably exceeded the combined ranges of the two parents. Hayes (1912) has found a similar case in the number of leaves in tobacco, and Emerson and East (1913) have seen the same phenomenon in the length of internode and total length of stalks in maize. It seems probable that such transgressive variation may be the rule rather than the exception when very complex characters are investigated; for it is hardly to be expected that a large number of plural determiners affecting such a character shall all act in the same direction or that the parent having the highest development of the given character shall generally contain all the genes which the other chosen parent possesses. Whenever such transgressive variability is producible by the genotypic recombinations of parental characters, the frequency with which F_2 individuals simulate either parent gives no clue to the total number of plural determiners which have been brought together, with respect to any character under consideration.

We might even derive a mathematical expression for the probability that the parents would stand at the extremes of total genetic variability, by assuming that the two parental types are taken at random. This would be perhaps a fair assumption, since the number of factors can not be determined by inspection. There would then be, if we let n represent the number of factors involved in the cross, $n!/2$ ways in which the event in question can not happen and only one way in which it can happen; hence the probability that all the factors would be present in the larger parent and absent in the lesser parent would be as 1 to $n!/2$. In the specific case of East and Emerson's corn, cited by Castle as having about 15 factorial differences, ($n=15$), there would be, therefore, 633,477,184,000 chances to one against all of these size-modifying factors being present in the larger parent and absent in the smaller parent. When we let $n=50$ or 150, to agree with the numbers indicated for the rabbit crosses, the chances become practically infinitesimal and we must fairly conclude that it has never happened, and never will happen, that a cross involving so many independent size differences has been made, or will be made, between individuals standing at the opposite extremes of the total potential genetic variability.

The remark made in my paper on duplicate genes, regarding the inadequacy of the frequency with which parental types are duplicated in the F_2 as an indication of the number of factors involved, applies equally well to the validity of conclusions drawn from changes in the F_2 standard deviations. The

correctness of this conclusion will be made sufficiently obvious by consideration of a simple illustrative case: Let us assume that there are involved in a given pair-mating the six duplicate size-factors, *AABBCCDDEEFF*, and their absences or corresponding recessives, *aabbccddeeff*. The relation of the F_1 and F_2 variability will be exactly the same no matter which of the four following types of mating is made: (a) *aabbccddeeff* $\times$ *AABBCCDDEEFF* (difference between parents, 12 units); (b) *AAbbccddeeff* $\times$ *aaBBCCDDEEFF* (parental difference, 8 units); (c) *AABBccddeeff* $\times$ *aabbCCDDEEFF* (parental difference, 4 units) or (d) *AABBCCddeeff* $\times$ *aabbccDDEEFF* (parental difference, zero). Neither Castle's original scheme nor Wright's suggested modification³ of it can be true, at one and the same time, for more than one of these types of mating and they have been specifically designed only for the first-mentioned type (a); but as we have seen in a previous paragraph, if the number of factors involved is large, the number of matings of type (a) is almost infinitesimal in comparison with the number of matings of the other types, (b) + (c) + (d) + (e) + . . . to n terms.

It is not necessary, however, to suppose that all factors which affect a blending character are additive. Indeed, it is quite certain that they are not, and that some factors act in a negative direction and others in a positive direction. Inhibiting and depressing factors have been fully demonstrated, as may be exemplified by such classic cases as the inhibitors of horn production in cattle and sheep; the inhibitor of indeterminate growth in the tail of the Japanese long-tailed fowl; the condensation factor characteristic of the *compactum* type of wheat; and a series of dominant depressing factors which Davenport's⁴ studies have made probable in the case of human statures. The fact that Castle himself was able to make progress in the minus direction in his selection experiments suggests the probable accumulation of factors acting in a negative direction, though in this case the evidence is not decisive, as the same effect would have been secured by the gradual elimination of factors acting in a positive direction. It seems to me that the combined action of plus-act-

³ Castle, W. E., "An Improved Method of Estimating the Number of Genetic Factors Concerned in Cases of Blending Inheritance," *Science*, 44: 223, Sept. 9, 1921.

⁴ Davenport, C. B., "Inheritance of Stature," *Genetics*, 2: 313-389. July, 1917.

ing and minus-acting growth factors gives a very true, though somewhat formal conception of the general situation in all organized beings;—the interplay of growth-promoting and growth-inhibiting factors may be thought of, in a figurative sense, as forming, within the limits of fluctuating variation, a sort of elastic “mold” into which any organism, whether plant or animal, develops, and which gives it its wonderful specificity of form and size.

But on the basis of this conception of factors, acting, some in a positive and some in a negative direction, the combined action of the negative group exactly balancing the combined action of the positive group, and jointly determining the mean size or the average condition with respect to any blending character which may be under consideration, it becomes unnecessary to assume the absence of dominance. I have been teaching my students for the past six years that the postulation of lack of dominance which has always been made the basis of the multiple-factor interpretation of inheritance of size or of other blending characters is wholly unnecessary and that those who have discussed this type of inheritance have been led to place an altogether unnatural and unwarranted stress on the occasional occurrence of incomplete dominance in other cases.

But whether any or all of the size-factors are dominant or not materially affects the amount of change which they effect in the value of the F_2 standard deviation, and must correspondingly change the estimate of the number of factors involved when that estimate is based on the value of these F_2 standard deviations. As a simple example, I may cite the hypothetical illustration given in my 1914 paper (p. 129), referred to above:

Thus, if a plant possessing a partial inhibitor or reducer of internode-number be crossed with another plant having a stimulator for internode length, all the other genes being the same in the two cases, the height of the F_1 plants would be intermediate between the heights of the parents, with variability due alone to fluctuation, as it is in the homozygous parents. The F_2 would show increased variability, and *this increase would appear greater if the two differentiating genes were dominant, than if dominance were absent.*⁵

To illustrate this fact further, let us assume that the six size-modifying factors which differentiate two mates are *AABBCC*, acting in the plus-direction, and *DDEEFF*, acting

⁵ Not italicized in the original.

in the minus-direction, and that the effect of each factor pair is represented by 2 units, thus making up the total of 12 units arbitrarily chosen by Castle. If the various permutations are worked out, the F_2 series of frequencies is found to be as follows:

TABLE I

DISTRIBUTION INTO SIZE-CLASSES RESULTING FROM THE INTERPLAY OF SIX FACTORS, 3 POSITIVE AND 3 NEGATIVE, WHEN DOMINANCE IS WANTING AND WHEN DOMINANCE IS COMPLETE.

Condition as to Dominance	Class Values and Frequencies													
	-6	-5	-4	-3	-2	-1	0	1	2	3	4	5	6	
No dominance	1	12	66	220	495	792	924	792	495	220	66	12	1	
Dominance complete	27		270		981		1,540		981		270		27	

These frequencies are exhibited graphically in Fig. 1, the curve produced by dominant factors being reduced to the same area as the curve of no dominance by dividing each frequency by 2. It is thus seen clearly that whether dominance is present or absent, the resulting curve is of the same general type.

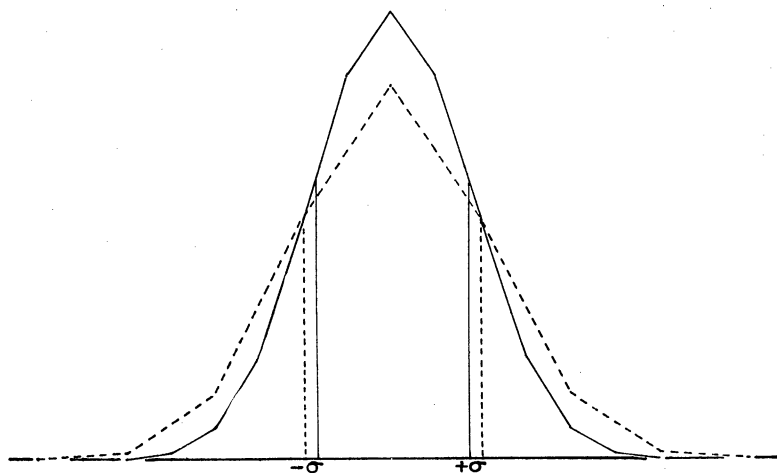


FIG. 1. The variation produced by six equivalent factors, three acting in plus direction and three in minus direction. The unbroken curve shows the result when dominance is wanting. Dotted curve shows the effect of complete dominance in all six factors.

The standard deviation of the curve with no dominance is $\sqrt{3} = 14.43$ per cent., as Castle has stated, but when all of the

six factors are completely dominant the standard deviation is $\sqrt{4.5}$, or 17.67 per cent., which is the percentage corresponding to 4 factors as given in Castle's Table II. In other words, six factors with dominance produce as great an increase in the F_2 variability as four factors would produce if none of them exhibited dominance.

It can be shown in the same way, by means of a simple test case, that Castle is entirely in error in saying that "if one factor really has an influence greatly superior to that of other factors in a case of blending inheritance, this will be seen in the production of asymmetrical or multimodal variation polygons in F_1 and F_2 ." The consequence he mentions would follow only in case the factor having the greater influence happened to be dominant, for in the absence of dominance each factor enters into combination with every other factor in a 1 : 2 : 1 series of intensities which gives the probable-error type of distributions. Thus, if we assume that four factor pairs *AABBCDD* differentiate two chosen mates with respect to some blending character, and that three of these factor pairs, *AABBCC*, each acts in a plus direction with a value of 2 units, and the fourth factor pair, *DD*, acts in a minus direction with a value of 6 units, the F_1 will be intermediate as before while F_2 will give the series of frequencies shown in Table II.

TABLE II

DISTRIBUTION INTO SIZE-CLASSES RESULTING FROM THE INTERACTION OF THREE FACTOR PAIRS ACTING IN THE PLUS DIRECTION, EACH ADDING TWO UNITS, AND A FOURTH FACTOR PAIR ACTING IN THE MINUS DIRECTION AND SUBTRACTING 6 UNITS

Condition as to Dominance	Class Values and Frequencies												
	-6	-5	-4	-3	-2	-1	0	1	2	3	4	5	6
No dominance	1	6	15	22	27	36	42	36	27	22	15	6	1
Dominance complete	3		27		81		82		9		27		27

It will be noted that while the curve of no dominance in this case is not quite a typical probable-error curve, it is nevertheless perfectly symmetrical and the deviations from the typical curve are such that they would never be detected when the several classes are modified by concurrent fluctuations from environmental causes.

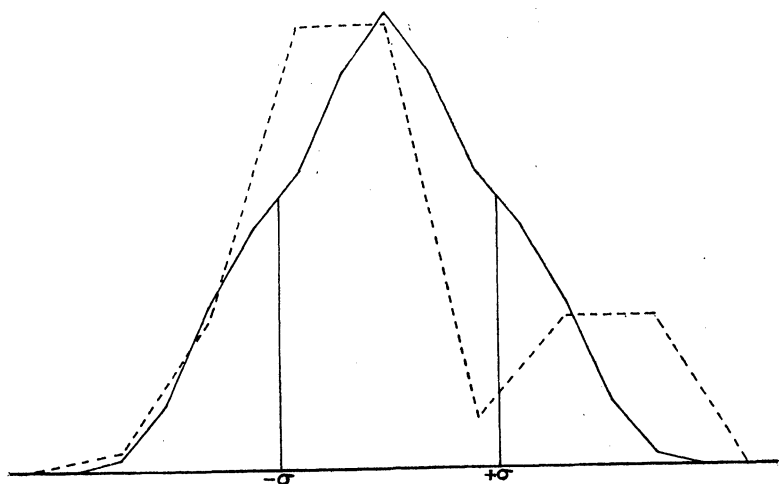


FIG. 2. Variation curve for four factors, three acting in plus direction, each with an effect of two units, and one acting in minus direction, with an effect equal to six units. Unbroken curve shows no dominance in any factor; dotted curve shows effect of complete dominance in all four factors.

The standard deviation of this series of values is $\sqrt{6}$, or the same as would be produced by 3 factors if all were of equal value, as shown in Castle's table. This curve is shown graphically in Fig. 2 together with the corresponding curve for factors weighted in the same manner, but exhibiting dominance. Such an irregular, multimodal curve as the latter would be easily detected if there were no fluctuating variations, but Castle apparently overlooks the effectiveness of fluctuating variations in obscuring the details of the underlying curve of genotypic variability. When he interpolates between the standard sizes of two breeds of rabbits 50 to 150 centers of genetic stability, he should take into account that the fluctuations about each of these centers will be sufficient to scatter the individuals which belong in any one class over quite a considerable number of other classes, thus filling up the gaps and hiding a great deal of putative multimodality in the genotypic curve, which would result from inequalities in the relative effectiveness of the several plural factors involved in any case of blending inheritance. Castle apparently thinks that this confusing concurrence of genetic and fluctuating variation could be dissolved to a certain extent by rearing "adequate numbers" in F_1 and F_2 , but it must not be forgotten that the masking effect of fluctuations advances *pari passu* with the increase in the size of the population. Only the irregularities due

to too small size of the random sample could be eliminated by the rearing of larger numbers; the effects of the interplay of numerous environmental factors could not be thus eliminated.

From the foregoing considerations it must be clear that Castle is altogether too sanguine as to the value of his method when he says:

It is perhaps not to be expected that results more than approximately correct would be given by this method, *unless fairly large numbers of both F_1 and F_2 individuals have been studied.*⁶

I believe the conclusion is justified that even a "fairly large" number of individuals of the F_1 and F_2 could not be expected to give correct estimates of the number of factors interacting in any case. As between the method of Castle in estimating the number of hypothetical duplicate factors operating in any case on the basis of the change they produce in F_2 standard deviations, and the method of Punnett, of formulating a genotypic situation on the basis of a small number of definitely weighted factors, I am convinced that the latter method is much to be preferred, even though it does not lend itself readily to a "general treatment of blending inheritance."

GEORGE H. SHULL

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DR. SHULL has kindly sent me his manuscript in advance of its publication and generously asks me to comment on it, an invitation which I gladly accept.

The difficulties which he thinks might be encountered in applying the method, which I have suggested, for estimating the number of genetic factors involved in cases of blending inheritance, seem to be essentially these.

1. The possible unequal influence of the several factors which are responsible for a case of blending inheritance, making it difficult to estimate their number from the total effect observed.
2. The possibility that some of the factors may be dominant in character and others not.
3. The possibility that some may be positive in action and others negative or inhibitive.

I think that these difficulties arise chiefly from the attempt of Dr. Shull to extend the application of the method beyond the field for which it was proposed. Cases of dominance or of trans-

⁶ Italics are mine.

gressive variation in F_2 would not come within the scope of blending inheritance as I defined it, when proposing the method, but only cases in which both F_1 and F_2 are intermediate between the parent races. But Dr. Shull maintains that some dominant *factors* may be involved even where dominant characters are not in evidence. This may be admitted as a possibility even though we have no evidence for it. What of it? Dr. Shull formulates a test case, the strongest one imaginable, in which *all* (six) factors affecting a size character are "completely dominant" and finds that in this case the method which I suggested would indicate a smaller number of factors than the true one, or four instead of six. If this is the maximum error to be anticipated when *all* factors are completely dominant, and it is really doubtful whether *any* factors are dominant in the case of blending characters, the possibility need not give us great concern. Further, if all factors involved in producing a character are "completely dominant," how can the character itself keep from being dominant? And if it is dominant, the case will be automatically removed from the field of blending inheritance. Shull seeks to avoid the difficulty in his hypothetical case by putting three dominant factors in one parent race and three in the other, but this arrangement, by recombination of factors, in F_2 would result in segregation of the parental types or in transgressive variation, either of which events would remove the case from the category of blending inheritance as I have defined it.

The supposed difficulty, that some factors involved in the production of blending characters may be positive in action while others are negative, is purely formal. With three positive and three negative factors, in his hypothetical case, Shull comes out with identically the same distribution in thirteen size classes that I calculated for the same number of factors all positive, both of us assuming no dominance to occur.

It remains to deal with the first-mentioned difficulty, the possible unequal influence of the several factors assumed to occur in blending inheritance. I had anticipated this difficulty in my first paper, but had assumed that, "if one factor really has an influence greatly superior to that of other factors in a case of blending inheritance, this will be seen in the production of asymmetrical or multi-modal variation polygons in F_1 and F_2 ."¹ Shull challenges this statement and artfully constructs a case to

¹ I should have limited the statement to F_2 .

disprove it in which the influence of one factor exactly equals and negatives that of three other factors. In this case he finds that the variation curve is symmetrical when no dominance occurs, but asymmetrical and bimodal otherwise. Had the hypothetical factors been less carefully weighted by Shull, he would not so easily produce a symmetrical F_2 curve. Consider an actual case in which a single factor of superior influence occurs and yet in which there is no dominance, that of the blue Andalusian fowl. Black mated with splashed white produces blue in F_1 , an apparent blending. Yet F_2 falls, as every one admits, into three distinct classes notwithstanding the occurrence of one or more modifying or inhibiting factors affecting the result in a minor degree (Lippincott). "Fluctuating variation" does not here obscure segregation, as Shull assumes would be true in hypothetical cases of blending inheritance in which factors of very unequal influence occur, even when large numbers are studied. Now I should not class the case of the Andalusian fowl as blending inheritance, but I think it may serve to show that Shull's objection is not well founded, in accordance with which he assumes that a factor of major influence will not be readily detected, even when it is operating in conjunction with minor modifying factors.

W. E. CASTLE

TO THE EDITOR OF THE AMERICAN NATURALIST: The foregoing article and rejoinder are submitted for publication in their original form. I do not think that Castle's "comment" adequately meets the several difficulties which I have pointed out, and he presents no considerations which seem to me to warrant a modification of the statements I have made. Others who are interested in the topic under discussion may be depended upon to recognize the validity or non-validity of any of the propositions made by either of us. It should be said, however, that there was nothing "artful" in my choice of an illustrative case to show that inequalities in the effectiveness of the several genes do not necessarily produce asymmetrical and multi-modal variation-polygons when dominance is not present. The case could have been made still more striking by using a larger number of factors, but the additional labor required did not seem necessary. Obviously Castle has not tried out cases in which the factors are weighted differently from the weightings I assigned to them,

or he would not say that in that case I "would not so easily produce a symmetrical F_2 curve."

That he has not assimilated the significance of the inter-play of plus-acting and minus-acting factors is shown by his question:

If all factors involved in producing a character are "completely dominant," how can the character itself keep from being completely dominant?

The curves in my Fig. 1 are an adequate answer to this question.

Finally, it seems hardly necessary to point out the inadequacy of the case of the Blue Andalusian fowl, as a proof that inequalities in genotypic variation are not masked by fluctuations when the amount of fluctuating variation is large in comparison with the distances between the centers of genetic stability which are determined by the numerous factor combinations putatively involved in the several examples cited in Castle's original paper.

GEO. H. SHULL

GENETIC TERMINOLOGY

THE genetic terms recently proposed by G. H. Shull¹ seem to supply a real need. Their general use would certainly tend to reduce both the danger of ambiguity and the need for cumbersome descriptive phrases. Probably a few additional numerical terms, such as *dizygous* and *trizygous*,² would also be useful. Some existing equivalents have an obvious disadvantage with respect to compounding; the compound *trichrosomal*, for example, could not replace *trizygous* ("dependent on three pairs of chromosomes"). *Monozygous* and *pleiozygous*, although often interchangeable with *linked* and *unlinked*, should be useful; the latter, for example, to characterize genes that are located in several pairs of chromosomes but are not all necessarily unlinked with each other. These words are so interrelated among themselves, and so closely related to terms in general use, that all their advantages can be realized with little effort.

Shull suggests that it is time "to abandon the use of 'Mendelian' and 'non-Mendelian' as definite categories, and to adopt

¹ Shull, George H., "Mendelian or Non-Mendelian?" *Science*, N. S., 54: 213-216. Sept. 9, 1921.

² For the Greek numeral prefixes see Blakeslee, Albert F., "Types of Mutations and their Possible Significance in Evolution," *AM. NATURALIST*, 55: 254-267. 1921.